ABCD position statement on haemoglobin A1c for the diagnosis of diabetes

ES Kilpatrick, PH Winocour*, on behalf of the Association of British Clinical Diabetologists (ABCD). Endorsed by the Association for Clinical Biochemistry (ACB)

Background
The diagnostic criteria for diabetes has slowly developed over the last 50 years. Fundamentally, the diagnosis of diabetes has been determined as the glycaemic threshold for microvascular disease, predominantly retinopathy. By the 1960s, the oral glucose tolerance test (OGTT) had become established as the means by which type 2 diabetes should be identified, but there was inconsistency as to how the test should be performed, in the quantity of glucose that should be ingested and the diagnostic blood glucose cut-offs. These criteria were standardised by the World Health Organization (WHO) in 1980 and have evolved since then, with the fast- ing plasma glucose (FPG) value more central to the diagnosis.2

Ever since the 1980s, when the measurement of haemoglobin A1c (HbA1c) became routine in patients already known to have diabetes, there has been the suggestion that this test could supplant the measurement of blood or plasma glucose as the diagnostic test for the disease. Two recent reports have recommended incorporating HbA1c into the current diagnostic criteria.3,4 This ABCD position statement updates these recommendations for the United Kingdom, highlighting the advantages and disadvantages to using HbA1c as a diagnostic test in non-pregnant individuals.

International recommendations
An International Expert Committee on the role of HbA1c in diabetes diagnosis published their report in June 2009.3 The Committee (comprising members appointed by the American Diabetes Association [ADA], the European Association for the Study of Diabetes [EASD] and the International Diabetes Federation [IDF]) recommended that diagnosis in type 2 diabetes should now usually be made solely on the basis of an HbA1c confirmed to be 6.5% (48mmol/mol), without the need to measure a plasma glucose concentration in the subject. A 'subdiabetic “high risk” state' would exist for subjects with an HbA1c of 6.0–6.4% (42–46mmol/mol).

Since then, the ADA has ratified the use of both the test and the diagnostic threshold as a fourth way of diagnosing diabetes, the other three continuing to be a fasting glucose value ≥7mmol/L, a 2hr post-OGTT value of ≥11.1mmol/L or, in someone with classic symptoms of diabetes, a random plasma glucose of ≥11.1mmol/L.4 The first three criteria would need confirmation by repeat testing in the absence of unequivocal hyperglycaemia. Where there is a discrepancy leading to one test (HbA1c or glucose) being diagnostic, but the other not, the ADA recommends retesting the raised test and diagnosing diabetes if it remains above the diagnostic threshold. The decision about which test to use is at the discretion of the health care professional. An individual is regarded as being at an increased risk of diabetes with an HbA1c of 5.7–6.4% (39–46mmol/mol).

Updated guidance from the EASD and WHO is awaited.

Using HbA1c to diagnose diabetes
The advantages and disadvantages are summarised in Table 1.

Advantages
No requirement for fasting. HbA1c has the undoubted benefit of being able to test an individual in the non-fasting state without it affecting the result. This could be helpful in the opportunistic identification of patients with glucose intolerance. Compared to glucose, there is also less of an issue in the stability of the measurement after a sample has been taken.

Low biological variability. Biological variability of HbA1c is less than fasting glucose and considerably less than the 2hr post-GTT glucose value (coefficient of variation 3.6% vs 5.7% in one study).5 This potentially means a single measurement is less likely to change significantly on repeat testing.

A measure of prior glycaemia. There is also the argument that, by giving an estimate of glycaemia over the preceding few weeks or months, HbA1c could provide a more complete view of glycaemia than a one-off fasting glucose or the ‘artificial’ conditions of an OGTT. It is also less affected by the stress hyperglycaemia that can be found during an acute concurrent illness.

Analytical considerations. For much of the time during which HbA1c has been in routine use in the UK it has been dogged by a lack of standardisation in measurement. This meant that results in patients with diabetes could...
vary substantially from one laboratory to another and having a single cut-off to diagnose the disease was inconceivable. From the mid 1990s, UK laboratories have steadily moved over to expressing results aligned to values used in the Diabetes Control and Complications Trial (DCCT-aligned) which has enabled more uniform reporting of HbA1c values nationally. Within the last year there has been the further refinement of calibrating laboratory instruments to the new IFCC standard for HbA1c measurement which, as well as heralding a change of units to mmol/mol, has the potential to bring results from different laboratories even closer together.

Disadvantages

Despite the steady advances in measuring HbA1c, inherent issues with the test mean that there is still potential for the test to give a misleading indication of glycaemia in an individual, and so lead to an inappropriate or missed diagnosis.

Abnormal haemoglobins. Measurement of HbA1c is dependent on the haemoglobin circulating being predominantly HbA. Being able to identify and account for abnormal haemoglobins depends on the particular HbA1c instrument being used, with most being able to discern some haemoglobinopathies but not others. The potential magnitude of this problem depends also on the prevalence of haemoglobinopathies, which obviously varies from race to race and country to country. As an example, data from the US estimate at least 10% of their 26 million African-American citizens have either an HbS or HbC trait present. Around one-third of HbA1c instruments in routine use there will give a clinically significant error in the presence of these haemoglobins, some without any indication that a problem might exist. Patients with haemoglobinopathies can also have altered red cell survival which will influence all HbA1c measurements. Guidance already exists on alerting clinicians to diabetes patients of African, Mediterranean or South-east Asian heritage who may have problems when using HbA1c for monitoring. The advice would also seem applicable if the test is to be used for diagnosis.

Anaemias. It is widely appreciated that haemolytic anaemia, from whatever cause, can lead to HbA1c values which are lower than expected because of reduced red cell survival. However, iron deficiency anaemia can lead to an inappropriate rise in HbA1c of 1–1.5%, which falls after iron treatment. This common condition, which is known to affect over three million women in the US, also seems to influence the HbA1c of non-diabetic subjects, although perhaps not as markedly as in those with the disease.

Patients with renal failure can demonstrate both iron deficiency and haemolytic anaemia, thereby having an unpredictable effect on the HbA1c result. Some instruments are also affected by the carbamylated haemoglobin formed in excess in renal failure.

Ageing and ethnicity. It has been identified that older non-diabetic subjects appear to have higher HbA1c values than younger individuals, being approximately 0.4% higher at 70 years than at 40 years, even after adjusting for fasting and 2hr glucose. Differences in the HbA1c have also been consistently found between individuals from different races, with Afro-Caribbeans having values 0.4% higher than Europids with apparently the same glucose tolerance. A similar difference has been found between individuals of South Asian descent and Caucasians in the UK. There is currently insufficient evidence to know if Afro-Caribbeans, Asians or elderly people are more hyperglycaemic than their GTT would suggest but, if not, then it is possible that these groups would be

### Table 1. Advantages and disadvantages to using plasma glucose and HbA1c

<table>
<thead>
<tr>
<th>Measure</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
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<tbody>
<tr>
<td>Fasting and/or post challenge glucose measures</td>
<td>• Established as the current means of diagnosing diabetes • Directly measures the molecule thought to cause diabetes complications • Not subject to misleading results due to non-glycaemic factors • Smaller differences in results between laboratories compared to HbA1c • Less expensive to measure than HbA1c</td>
<td>• Requires patient to be tested in the fasting state and for the sample to be analysed promptly • May require a glucose tolerance test for diagnosis • A measurement of glucose at a single time-point • Higher within-individual variability than that of HbA1c • Oral glucose tolerance testing laborious and time consuming</td>
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<tr>
<td>HbA1c</td>
<td>• Established as a means of monitoring patients already known to have diabetes • Does not require a fasting sample and is more stable after sample collection than glucose • A marker of glucose control over the previous weeks/months • Lower within-individual variability than that of glucose • Although more costly than glucose, overall cost as part of a screening/diagnostic pathway may not be so high</td>
<td>• Measurement can be misleading in patients with haemoglobinopathies, anaemia or renal failure • May differ between patients of different ages and ethnicity • Larger differences in results between laboratories compared to glucose • A surrogate marker of hyperglycaemia with between-individual discrepancies between glucose and HbA1c</td>
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over-diagnosed by a single HbA1c cut-off. In turn, this could necessitate the use of age-related and race-related diagnostic thresholds for HbA1c.

**Analytical considerations.** Although IFCC standardisation of HbA1c measurement is an undoubted step forward in improving comparability between laboratories, the technologi-
cal limitations of measuring HbA1c mean there are still clinically signifi-
cant differences between laboratories using different instruments from different manufacturers. As part of the UK National Quality Assurance Scheme (NEQAS), the same sample sent to UK laboratories was analysed on 251 instruments in July 2009. The assigned HbA1c value was the proposed diagnostic threshold of 6.5% (48mmol/mol), but reported results varied from 5.8 and 7.2% (40 and 55mmol/mol) [personal communic-
ation, Jonathan Middie, UKNEQAS], so the likelihood of being diagnosed with diabetes, or not, would still be partly dependent on the laboratory to which the sample was sent. Currently, most point-of-care HbA1c analysers do not perform satisfactorily enough to be used for diagnostic purposes.

**Comparing HbA1c and glucose to diagnose diabetes**
The relationship between fasting/2hr glucose and HbA1c within the non-
diabetic reference range is not nearly as tight as it is when patients with dia-
abetes are included (r² =0.26 for FPG and 0.14 for 2hr16), so the population of individuals diagnosed using HbA1c is not the same as that using glu-
cose. Using an HbA1c threshold which will maintain an similar prevalence of diabetes to that currently, only around a half would be diagnosed using both criteria. Consequently, half the subjects diagnosed at present using glucose would not be using HbA1c, and half using HbA1c would not currently be using glucose.

The proposed diagnostic cut-off of 6.5% (48mmol/mol) for HbA1c is above the value that most studies have shown would lead to a diabetes preva-
ience equivalent to that using plasma glucose, so fewer patients will be newly diagnosed if HbA1c at this level is used alone. In the US NHANES population, 1.6% of adult individuals had undiagnosed diabetes using this HbA1c threshold, 2.5% if using fasting glucose alone and 4.9% if using 2hr glucose alone.15 The prevalence of undiagnosed diabetes using any glucose criteria (fasting or 2hr) was 5.1%, and including HbA1c it rose to 5.4%. There is thus more than a three-fold difference in prevalence between the preferred position of the Expert Committee (1.6%) and both the current WHO recommendation (5.1%) and the literal interpretation of the ADA recommendation to use any or all of the tests (5.4%).

Overall, only 25% of individuals with a ‘positive’ OGTT had an HbA1c ≥ 6.5%, while 45% of individuals who exceeded both the fasting and 2hr glucose criteria (1% of the full popula-
tion) were not diagnosed with diabetes using HbA1c.

Superimposing the effect of eth-
nicity and ageing has a marked influ-
ence on these proportions. Whitehall II data from the UK showed that while 91% of white subjects with an HbA1c ≥ 6.5% had diabetes by GTT, the higher values normally found in Asian and black subjects meant that only 61% and 50% respectively also had glucose diagnosed diabetes.18 The rise in HbA1c normally with age is probably responsible for only 15% of elderly patients with an HbA1c ≥ 6.5% in the Rancho Bernardo Study having glucose-defined diabetes and one-third actually being completely normoglycaemic above this HbA1c.19

**HbA1c as a test to identify risk of microvascular complications**
Identifying patients at risk of develop-
ing microvascular complications (particularly retinopathy) has been the basis for diagnosing an individual as having diabetes. The International Expert Committee argued it was more appropriate to use ‘moderate’ retinopathy (rather than ‘any’) as an endpoint in identifying an HbA1c threshold for diabetes,3 which is presumably one reason why the prevalence of diabetes using the 6.5% (48mmol/mol) value derived in this way is so much lower than when using current glucose criteria. However, using this logic, the glucose cut-offs may have been expected to rise too.

There is debate around whether HbA1c predicts retinopathy in a population any differently to that of glucose. Older studies (in Pima Indians, Egyptian and NHANES pop-
ulations) seemed to favour glucose as the best predictor,20 particularly the 2hr value, while as-yet unpublished data cited in the Expert Committee report has shown HbA1c to be at least as predictive.3

**HbA1c as a test to identify risk of macrovascular complications**
The diagnosis of diabetes leads to intensive management of cardiovascu-
lar (CV) risk factors in addition to hyperglycaemia, with many patients prescribed antihypertensive and lipid lowering agents. As shown, at a 6.5% cut-off far fewer individuals in some populations would automatically receive this treatment consideration. In addition, the move to HbA1c for diagnosis would largely replace the 2hr post-OGTT glucose diagnosis of diabetes and therefore remove impaired glucose tolerance (IGT) as an entity. HbA1c is acknowledged to be poor at identifying patients with impaired fasting glucose (IFG) or IGT,21 and those individuals found to be in the Expert Committee ‘high risk’ state (HbA1c of 6.0–6.4% [42–46mmol/mol]) belong to a group which is about 10 times smaller in size than would be identified as having either IFG or IGT.17 The alternative categorisation of intermediate glucose intolerance will therefore have a major impact on both CV disease risk estima-
tion and the strategy for ongoing screening for diabetes in this group.

With regard to CV risk prediction, there is evidence that HbA1c may be superior to fasting glucose alone in predicting future CV events.22 However, post-prandial hypergly-
caemia, even with all its inherent variability, has usually been shown to be superior, again compared to both fasting glucose and HbA1c.23 Other studies have also shown a relationship between increasing HbA1c and increas-
ing CV risk,24 but the test appeared to add little to the CV risk already identi-
fied using known risk factors such as blood pressure and cholesterol.25

**Type 1 diabetes**
Although the discussion around using HbA1c for diagnosis centres on type 2 diabetes, the ADA also makes it
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**Table 2. Suggested diabetes screening algorithm for the UK**

1. Consider laboratory testing of HbA1c as an alternative test in adults without conditions known to affect HbA1c measurement. Do not use if type 1 diabetes is suspected
2. If HbA1c <5.8% (40mmol/mol) then diabetes excluded
3. If HbA1c >7.2% (55mmol/mol) on 2 occasions then diabetes diagnosed*
4. If HbA1c 5.8–7.2% (intermediate HbA1c), or an HbA1c >7.2% is not confirmed, use existing fasting glucose and/or glucose tolerance test criteria to confirm or exclude diabetes
5. Where HbA1c measurement may be, or is known to be, inappropriate, test using existing fasting glucose and/or glucose tolerance test criteria
6. Annual testing is suggested for patients identified as having intermediate HbA1c, IFG or IGT on initial screening

*Repeat testing can be at any time after the initial request and is mainly to ensure a sample mix-up could not have occurred.

Applicability of HbA1c limitations in known diabetes

The disadvantages of HbA1c in diabetes diagnosis also apply to patients with known diabetes where population HbA1c targets are used to inform management of hyperglycaemia. However, ABCD’s view is that there is a distinction in using HbA1c for diagnosis and for monitoring. Firstly, for an individual subject a diagnosis of diabetes often has lifelong major lifestyle, insurance and psychological implications as well as meaning they will be recommended to use the health care system much more frequently than before diabetes was identified. There is, therefore, an especial duty to patients to ensure that there is the least chance of misdiagnosing hyperglycaemia, one way or the other. By doing so, it also makes sure that health care resources are targeted in the most appropriate way. Secondly, while there may be an argument that race and age-specific HbA1c targets be considered for patients with diabetes, these measurements are often supported by that of blood glucose, so discrepancies between them can usually be identified. Lastly, the magnitude of the discrepancy in diabetes will likely, at worst, mean a treatment change is considered sooner or later than is ideal; however, when applied to using HbA1c as a diagnostic test it could, as shown above, lead to either incorrect diagnosis in some normoglycaemic subjects or false reassurance – and therefore a missed diagnosis – in some with unequivocal hyperglycaemia.

Alternative HbA1c strategies

Glucose measurement will always need to be an option for diagnosing diabetes, either because HbA1c is known to be unreliable in an individual or because the health care budget is not support HbA1c measurement.

Options for incorporating HbA1c into the diagnostic process other than replacing glucose have been suggested. One option has been to combine measurement of fasting glucose and HbA1c, meaning that HbA1c is being used as a surrogate for the 2hr post-GTT result. An added attraction is the recent evidence that increasing fasting glucose and HbA1c are both independently predictive of subsequent diabetes development. By combining the two tests it has been shown that this could obviate the need for around half of current OGTTs. Another suggestion has been to make the HbA1c thresholds for ruling out or ruling in diabetes lower and higher than suggested by the ADA in order to triage patients for further glucose testing. By using a ‘rule out’ HbA1c cut-off of ≤5.5% (37mmol/mol) and a ‘rule in’ threshold of ≥7.0% (53mmol/mol), three-quarters of the AusDiab population could be excluded from further investigation. A further analysis of these data has shown that a ‘rule out’ threshold of ≤5.8% (40mmol/mol) would still have a negative predictive value of 98.3% and a ‘rule in’ cut-off of ≥6.7% (50mmol/mol) would have a positive predictive value of 100%, leaving 10% of the population (HbA1c 5.8–6.7% [40–50mmol/mol]) requiring glucose testing to confirm or refute hyperglycaemia [personal communication, Lu Zhong]. The applicability of these thresholds to populations of different ages and races and to individuals in the UK has yet to be established. Since ageing, ethnicity and iron deficiency all appear to raise HbA1c, it means the uncertainty mainly involves the ‘rule in’ threshold. ABCD would therefore suggest the testing principle given in Table 2, being aware that the limits may need to change when further data become available.

Research agenda

In considering HbA1c as a diagnostic test for diabetes in the UK we suggest the following key areas for research:

- Continued industry and laboratory initiatives to bring HbA1c values in UK laboratory analysers from different manufacturers closer to both the IFCC reference HbA1c method and to one another.
- Further examination of any effect of ageing and ethnicity on HbA1c values in the UK population.
- Exploration of desirable UK thresholds for a ‘rule in, rule out’ strategy using HbA1c which will account for any effect of ageing or ethnicity on these values.
- Comparing HbA1c as a predictor of retinopathy with the current UK strategy of fasting glucose values possibly cascading on to a GTT.

Conclusions

ABCD can understand the appeal of using HbA1c as a diagnostic test for diabetes and of the practical advantages it confers compared to glucose
measurement. The current glucose criteria for diagnosis remain somewhat arbitrary and the testing process itself has well documented limitations. However, at this moment, there are unresolved concerns which could feasibly lead to HbA1c being much more likely than glucose to completely misdiagnose an individual as having diabetes or not. The possible requirement for further testing to exclude conditions such as anaemia or haemoglobinopathies, as well as having to account for patient age and ethnicity, may make the simplification of diagnosis using HbA1c measurement alone anything but.

ABCD recommends against using HbA1c to diagnose when type 1 diabetes is suspected, appreciating that this statement is complicated by the difficulty in sometimes distinguishing type 1 from type 2 diabetes at initial presentation.

For type 2 diabetes, the complete summarizing of a plasma glucose diagnosis with HbA1c seems premature given current evidence. However, there may be potential for using a laboratory-measured HbA1c to triage patients for further glucose testing or to be used in combination with fasting glucose in diagnosis. The feasibility of using either of these successfully in a UK population is a research priority. Subjects with conditions known to affect HbA1c values would still require exclusion (Table 3). For others, if HbA1c is to be used in a diagnostic algorithm, ABCD recommends that current plasma glucose criteria be used to confirm or exclude diabetes in patients with equivocal HbA1c values.

**Conflict of interest statement**

There are no conflicts of interest.

**References**